A novel biomarker-based prognostic score in acute ischemic stroke: The CoRisk score

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Abstract: OBJECTIVES To derive and externally validate a copeptin-based parsimonious score to predict unfavorable outcome 3 months after an acute ischemic stroke (AIS). METHODS The derivation cohort consisted of patients with AIS enrolled prospectively at the University Hospital Basel, Switzerland. The validation cohort was prospectively enrolled after the derivation cohort at the University Hospital of Bern and University Hospital Basel, Switzerland, as well as Frankfurt a.M., Germany. The score components were copeptin levels, age, NIH Stroke Scale, and recanalization therapy (CoRisk score). Copeptin levels were measured in plasma drawn within 24 hours of AIS and before any recanalization therapy. The primary outcome of disability and death at 3 months was defined as modified Rankin Scale score of 3 to 6. RESULTS Overall, 1,102 patients were included in the analysis; the derivation cohort contributed 319 patients, and the validation cohort contributed 783. An unfavorable outcome was observed among 436 patients (40%). For the 3-month prediction of disability and death, the CoRisk score was well calibrated in the validation cohort, for which the area under the receiver operating characteristic curve was 0.819 (95% confidence interval [CI] 0.787-0.849). The calibrated CoRisk score correctly classified 75% of patients (95% CI 72-78). The net reclassification index between the calibrated CoRisk scores with and without copeptin was 46% (95% CI 32-60). CONCLUSIONS The biomarker-based CoRisk score for the prediction of disability and death was externally validated, was well calibrated, and performed better than the same score without copeptin. CLINICALTRIALSGOV IDENTIFIER NCT00390962 (derivation cohort) and NCT00878813 (validation cohort).

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ARTICLE

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Abstract

Objectives

To derive and externally validate a copeptin-based parsimonious score to predict unfavorable outcome 3 months after an acute ischemic stroke (AIS).

Methods

The derivation cohort consisted of patients with AIS enrolled prospectively at the University Hospital Basel, Switzerland. The validation cohort was prospectively enrolled after the derivation cohort at the University Hospital of Bern and University Hospital Basel, Switzerland, as well as Frankfurt a.M., Germany. The score components were copeptin levels, age, NIH Stroke Scale, and recanalization therapy (CoRisk score). Copeptin levels were measured in plasma drawn within 24 hours of AIS and before any recanalization therapy. The primary outcome of disability and death at 3 months was defined as modified Rankin Scale score of 3 to 6.

Results

Overall, 1,102 patients were included in the analysis; the derivation cohort contributed 319 patients, and the validation cohort contributed 783. An unfavorable outcome was observed among 436 patients (40%). For the 3-month prediction of disability and death, the CoRisk score was well calibrated in the validation cohort, for which the area under the receiver operating characteristic curve was 0.819 (95% confidence interval [CI] 0.787–0.849). The calibrated CoRisk score correctly classified 75% of patients (95% CI 72–78). The net reclassification index between the calibrated CoRisk scores with and without copeptin was 46% (95% CI 32–60).

Conclusions

The biomarker-based CoRisk score for the prediction of disability and death was externally validated, was well calibrated, and performed better than the same score without copeptin.

ClinicalTrials.gov identifier

NCT00390962 (derivation cohort) and NCT00878813 (validation cohort).

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Glossary

ASTRAL = Acute Stroke Registry and Analysis of Lausanne; **AUC** = area under the receiver operating characteristic curve; **CI** = confidence interval; **CoRisk** = Copeptin for Risk Stratification in Acute Stroke Patients; **COSMOS** = Copeptin in Osmoregulation and Stress Assessment; **JURaSSIC** = Clinician Judgment Versus Risk Score to Predict Stroke Outcomes; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NRI** = net reclassification index; **PLAN** = preadmission comorbidities, level of consciousness, age, and neurologic deficit; **SOAR** = stroke subtype, Oxfordshire Community Stroke Project, age, and prestroke modified Rankin Scale; **THRIVE** = Totaled Health Risks in Vascular Events; **VISTA** = Virtual International Stroke Trials Archive.

One of the first questions asked by relatives and patients admitted to the emergency department with an acute ischemic stroke relates to their prognosis. Early and accurate prognostication can individualize counseling, guide triage, and inform end-of-life decisions.

A contemporary prognostic score should take into account whether the patient is treated with intravenous or endovascular recanalization therapy because this affects outcome.[1,2] This would allow computation of 2 probabilities of unfavorable outcome, conditional on thrombolysis. However, the variables for acute treatment are lacking in the most prominent current prognostic scales.[3] Moreover, to be used in the emergency clinical setting, a prognostic score should be parsimonious, that is, encompass a low number of items, all fast and easy to assess. One of the leanest scores contains only 2 variables, age and NIH Stroke Scale (NIHSS) score, and was validated in the Virtual International Stroke Trials Archive (VISTA). The score achieved an area under the curve of 0.81 for disability and of 0.71 for mortality 3 months after stroke.[4] Such figures can be improved. First, recanalization therapy status should be accounted for. Second, blood markers may increase the prognostic accuracy of scores. Recently, copeptin plasma levels measured on admission to the emergency room were associated with disability and mortality at 3 months, after adjustment for age, stroke severity, size of the ischemic lesion, and other outcome predictors.[5,6] Our aim was to derive and validate a novel biomarker-based parsimonious score for use in the emergency room using copeptin, one of the most promising prognostic blood biomarkers in patients with acute ischemic stroke.

Methods

Standard protocol approvals, registrations, and patient consents

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the ethics committees. All patients or their welfare guardians provided written informed consent for the collection of data and blood samples and subsequent analyses.

Patients

The derivation and validation cohorts have been described previously.[5,6] Briefly, the derivation cohort consisted of consecutive patients with acute ischemic stroke hospitalized at the University Hospital Basel, Switzerland, between 2006 and 2007 (Copeptin in Osmoregulation and Stress Assessment [COSMOS] study, ClinicalTrials.gov identifier NCT00390962). The validation cohort consisted of consecutive patients with acute ischemic stroke hospitalized at the University Hospital Bern and University Hospital Basel (Switzerland) and at the Goethe University Hospital Frankfurt a.M. (Germany) between 2009 and 2011 (Copeptin for Risk Stratification in Acute Stroke Patients [CoRisk] Study, ClinicalTrials.gov identifier NCT00878813). In both cohorts, acute ischemic stroke was defined as an acute focal neurologic deficit lasting >24 hours with no sign of acute intracranial bleeding on cerebral imaging.[7] Both patients with and those without thrombolysis were included. Thrombolysis was defined as either intravenous or endovascular treatment. Patients lost to follow-up were excluded from the present analysis.

Copeptin measurements

In both the COSMOS and CoRisk studies, blood was drawn in the emergency room on patient admission. In the COSMOS study, blood was drawn within 24 hours of stroke onset in 322 patients; we excluded 40 patients from COSMOS in whom blood was drawn between 24 and 72 hours.[5] In the CoRisk Study, no patient admitted beyond 24 hours of symptom onset was included, so blood was drawn within 24 hours in all patients in the emergency room (783 of 783).[6] In both cohorts, blood was always drawn before thrombolysis if performed. Among patients treated with thrombolysis, an additional venipuncture was performed the day after admission, and copeptin levels were again assessed. After centrifugation for 20 minutes at 3,000*g* at room temperature, plasma was aliquoted from EDTA tubes. Tubes were frozen locally at each center at −70°C. Copeptin levels were assessed in plasma in a blinded batch analysis. Copeptin was measured by a chemiluminescence sandwich immunoassay, the specifics of which have been reported elsewhere.[8] In 359 healthy individuals, median copeptin levels were reported to be 4.2 pmol/L with a 99th percentile of 13.5 pmol/L.[8]

Endpoints

In both cohorts, trained vascular neurologists and study nurses assessed outcome 3 months after acute stroke either during an outpatient visit (for patients who underwent thrombolysis) or with a structured follow-up telephone interview. They were blinded to copeptin levels and baseline

clinical variables, including patient demographics and treatment.[5,6]

In both cohorts, the 2 primary endpoints were unfavorable functional outcome and death, defined as a modified Rankin Scale (mRS) score of 3 to 6, and mortality 3 months after stroke onset.[5,6]

Statistics

Two logistic regression models were fitted: one for modeling unfavorable functional outcome or mortality (mRS score 3–6) vs favorable functional outcome (mRS score ≤2) and a second one for modeling mortality vs survival within 3 months after stroke.

As a first step, we used only age, NIHSS score on admission, and thrombolysis as variables in the logistic regression model. Subsequently, we added $\log_{10}$-transformed copeptin levels. The reason we chose age, NIHSS score, and copeptin as covariates was that they were the only 3 variables that were independently associated with 3-month functional outcome and mortality in both the derivation and validation cohorts.[5,6] The reason for including thrombolysis was its evidence on outcome improvement (Class I, Level A).[9] In every model, we confirmed that there was no indication of a nonlinear effect for copeptin, age, NIHSS score, or thrombolysis using multivariable fractional polynomials.

When an existing model is transferred to another population with a different prevalence of the event, the predicted probabilities might be systematically too low or too high; that is, there is an error in calibration.[9] Calibration was assessed by calibration curves for which predicted probabilities are plotted against true probabilities for grouped observations. Grouping of observations is necessary to derive true probabilities from patients' status by taking the relative frequency of the class of interest in that group. We used an average number of 40 observations per group to generate the figure with the calibration curves. In the case of perfectly calibrated probabilities, all observations lie on the 45° diagonal. Both models were recalibrated for logistic regression.[10] In this approach, a logistic regression model was built on the COSMOS data first, and the regression coefficients were fixed. Then, the intercept was estimated anew with the CoRisk data (validation cohort) and 10-fold cross-validation while all other regression coefficients were kept unchanged. We called the calibrated model with $\log_{10}$ (copeptin), age, NIHSS score, and thrombolysis the CoRisk score. The Brier score[11] was used to measure prediction performance. The Brier score is the mean of the squared difference between patient status and predicted probability. Thus, small values for the Brier score indicate good prediction accuracy. To assess the discriminative value of the model with and without copeptin, the area under the receiver operating characteristic curve (AUC) was calculated and compared. To identify clinically meaningful copeptin cutoffs, we proceeded as follows. First, in the derivation cohort, we identified cutoffs with a sensitivity of ≥80% and the highest specificity and cutoffs with a specificity of ≥80% and the highest sensitivity. Then, in the validation cohort, we computed the sensitivity and specificity of such cutoff values. To assess the statistical significance of the AUC change between the model without copeptin vs the model with copeptin, we used the likelihood ratio test as recommended for nested regression models.[12] The continuous net reclassification index (NRI) was calculated from the proportions of individuals with increased and decreased predicted probability when the predictions of 2 models, with and without copeptin, are compared.[13] Two-sided values of $p < 0.05$ were considered significant.

We used the statistical software R 3.3.0 for analysis. The R package mfp was used for calculating multivariable fractional polynomials; the R package rms was used for plotting the calibration curves; the R package ROCR (R package version 1.0–7) was used for calculating the AUC; and the R package Hmisc was used for calculating the NRI.

Results

Overall, a total of 1,102 patients were included in the analysis. The derivation cohort contributed 319 patients, and the validation cohort contributed 783 patients. Patients lost to follow-up were excluded (derivation cohort 3 patients, validation cohort 5 patients). The reasons for loss to follow-up were unclear. The 2 cohorts were geographically independent: in the derivation cohort, all patients were admitted to the University Hospital Basel (Switzerland); in the validation cohort, 740 patients (95%) were admitted to the University Hospital Bern (Switzerland), 25 (3%) to Goethe University Hospital Frankfurt a.M. (Germany), and 18 (2%) to the University Hospital Basel. The baseline characteristics of the 2 cohorts are summarized in table 1. In the derivation cohort, 65 patients (20%) were treated with thrombolysis (intravenous thrombolysis [n = 59, 91%], endovascular treatment [n = 6, 9%], intravenous and endovascular treatment [n = 0, 0%]). In the validation cohort, 318 patients (41%) were treated with thrombolysis (intravenous thrombolysis [n = 160, 50%], endovascular [n = 123, 39%], intravenous and endovascular [n = 35, 11%]).

At 3 months, unfavorable outcomes were observed in 136 patients (43%) of the derivation and 300 patients (38%) of the validation cohort. The original score and the CoRisk score (i.e., the recalibrated original score) are reported in table 2, and the respective calibration curves are displayed in figure 1. The CoRisk score showed good congruence between predicted and observed 3-month functional outcome. The formula to predict unfavorable 3-month outcome is reported in table 3, along with 2 examples. As convenience tools, an online calculator and Android app are available.[14,15] The sensitivity and specificity of copeptin cutoff values are reported in table 4. Adding copeptin to the calibrated model with age, NIHSS score, and thrombolysis increased the area

Table 1 Patient characteristics in the derivation (COSMOS) and validation (CoRisk) cohort

	Derivation cohort (n = 319)	Validation cohort (n = 783)
Age, median (IQR), y	75 (64–83)	71 (60–80)
NIHSS score, median (IQR)	5 (3–10)	6 (3–13)
Thrombolysis, n (%)	65 (20)	318 (41)
Copeptin, median (IQR), pmol/L	12.2 (6.0–24.3)	14.2 (5.9–46.5)
Total anterior circulation syndrome, n (%)	37 (12)	158 (20)
Modified Charlson comorbidity index score, median (IQR)	1 (0–2)	0 (0–1)
C-reactive protein, median (IQR), mg/L	3.2 (3.0–8.8)	3.0 (3.0–6.0)
Blood glucose, median (IQR), mmol/L	6.1 (5.5–7.4)	6.3 (5.5–7.5)
Stroke onset to venipuncture <3 h, n (%)	78 (24)	359 (46)
3-mo follow-up, n (%)		
Unfavorable functional outcome[a]	136 (43)	300 (38)
Mortality	38 (12)	118 (15)

Abbreviations: IQR = interquartile range; CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients; COSMOS = Copeptin in Osmoregulation and Stress Assessment; NIHSS = NIH Stroke Scale.
[a] Unfavorable functional outcome at 3 months was defined as a modified Rankin Scale score of 3 to 6, meaning disability or death.

under the curve from 0.816 (95% confidence interval [CI] 0.785–0.846) to 0.819 (95% CI 0.787–0.849, $p_{\text{likelihood ratio test}} < 0.001$, figure 2); that is, the probability that the CoRisk score assigns a higher probability for an unfavorable 3-month outcome to patients with an unfavorable outcome than to patients with a favorable outcome is 81.9%. Overall, 75% (95% CI 72%–78%) of patients were classified correctly. At a CoRisk score cutoff of 0.43 (or 43% of estimated probability of unfavorable outcome at 3 months), the sensitivity was 67% (95% CI 62%–72%) and specificity was 80% (95% CI 76%–83%).

The overall NRI between the calibrated models without and with added copeptin levels was 0.46 (95% CI 0.32–0.60). Among those patients with a good 3-month functional outcome, a net of 0.35 (95% CI 0.26–0.43) was moved to a lower risk-category; among those with an unfavorable outcome, a net of 0.11 (95% CI 0.001–0.23) was moved to a higher risk category. Among patients treated with thrombolysis, the change in copeptin blood levels before and after thrombolysis was not associated with 3-month outcome in either the derivation or validation cohort (data not shown).

Death within 3 months occurred in 38 patients (12%) of the derivation and 118 patients (15%) of the validation cohort. The calibration plot in figure 3 shows that the logistic regression model with age, NIHSS score, copeptin, and thrombolysis did not fit well. Recalibration could not improve the model fit; therefore, the model was not accurate for the prediction of mortality at 3 months.

Table 2 Estimated regression coefficients of the original and recalibrated model (CoRisk score) predicting unfavorable functional outcome[a] at 3 months

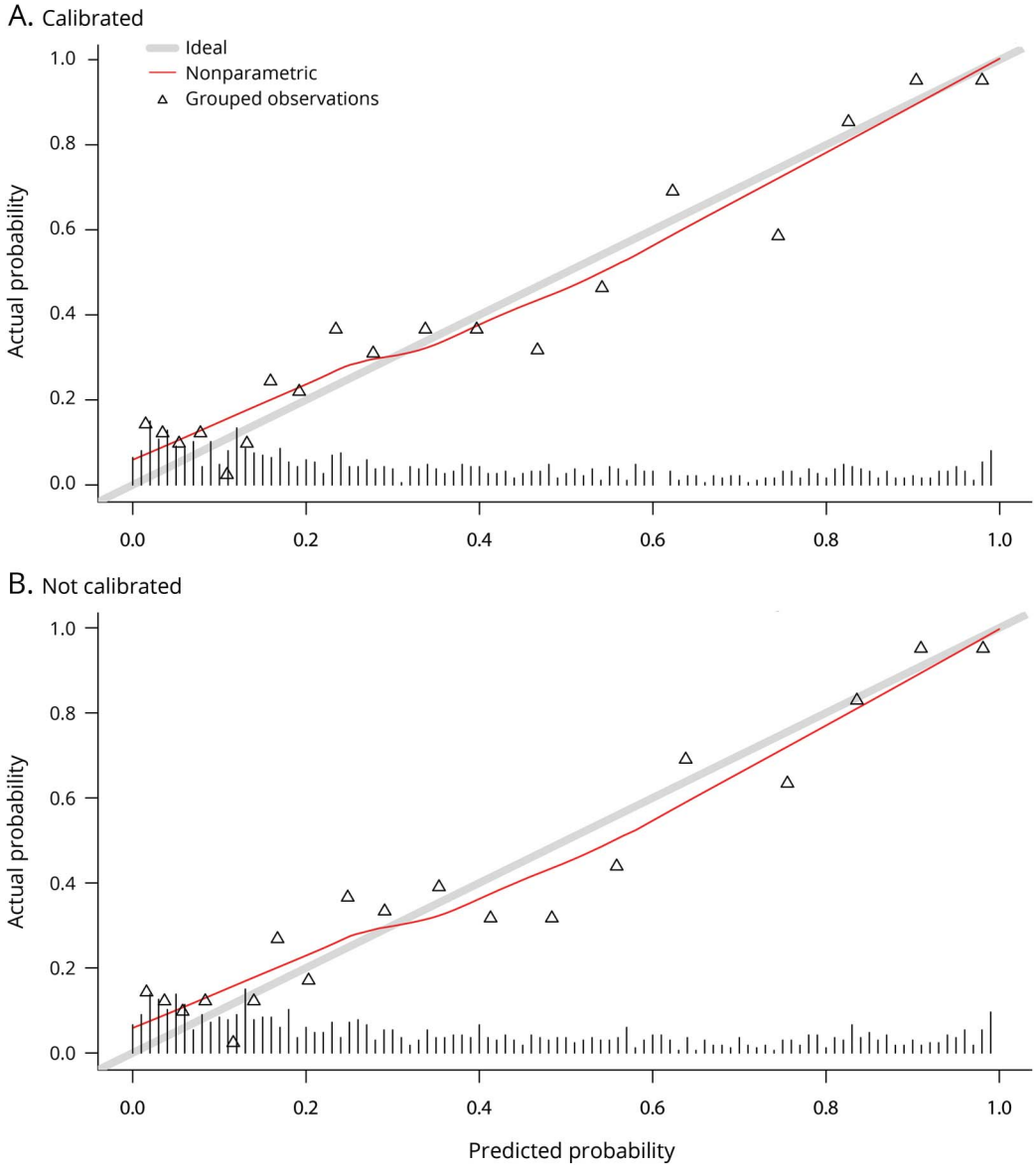
	Original	Standard error	CoRisk score
Intercept	−7.131	1.123	−7.202
Age	0.057	0.013	0.057
NIHSS	0.220	0.035	0.220
Thrombolysis	−2.054	0.531	−2.054
Log_{10} (copeptin)[b]	1.185	0.357	1.185

Abbreviations: CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients; NIHSS = NIH Stroke Scale.
[a] Unfavorable functional outcome at 3 months was defined as a modified Rankin Scale score of 3 to 6, meaning disability or death.
[b] Copeptin expressed in pmol/L.

Discussion

The CoRisk score could be derived and externally validated in a geographically and chronologically independent cohort. The novel features of the CoRisk score are the inclusion of a validated prognostic blood marker, copeptin, and thrombolysis to predict functional outcome 3 months after an ischemic stroke. Conditional on thrombolysis status, the CoRisk score allows computation of 2 distinct probabilities of 3-month disability. Albeit statistically significant, the numeric increase in the AUC curves between the predictive models without and with copeptin was modest. At the same time, the inclusion of copeptin in the model was associated with an NRI of 46%, indicating that copeptin allowed improvement in risk reclassification in almost every second patient. This improvement is clinically relevant when it comes to accurately

Figure 1 Calibration curves for the original model and recalibrated model (CoRisk score) for the prediction of unfavorable functional 3-month outcome



(A) Calibrated and (B) not calibrated. CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients.

estimate prognosis, on which triage decisions, acute management decisions, and end-of-life decisions are based. However, for the prediction of death vs survival, the model was not well calibrated, so we were not able to provide an accurate score for the second outcome measure.

Including thrombolysis in the CoRisk score accounts for the progress made in the last 2 decades in the treatment for acute ischemic stroke.[1,2] An item for thrombolysis was lacking in all of the 8 prognostic scores published in leading clinical journals since 2000 and compared head to head in 2017.[3] The prognostic scores were Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score; iScore; iScore-revised; preadmission comorbidities, level of consciousness, age, and neurologic deficit (PLAN); stroke subtype, Oxfordshire Community Stroke Project, age, and prestroke modified Rankin Scale (SOAR); modified SOAR; Stroke Prognosis Instrument 2; and Totaled Health Risks in Vascular Events (THRIVE).[3] In the derivation and validation studies of the 8 prognostic scores, patients treated with thrombolysis were not explicitly excluded, with the exception of PLAN. In PLAN, patients treated with thrombolysis were excluded from the primary analysis and assessed in a post hoc analysis, which revealed a reduced prognostic accuracy among patients treated with thrombolysis ($AUC_{no\ thrombolysis}$ = 0.77 vs $AUC_{thrombolysis}$ = 0.72). The reduction in prognostic accuracy likely results from thrombolysis affecting outcomes, thus complicating prognostication if not accounted for.

Table 3 CoRisk score for the prediction of unfavorable 3-month outcome

Probability of unfavorable 3-month outcome = $\frac{1}{1+e^{7.202-0.057\,(\text{Age in years})-0.220\,(\text{NIHSS points})+2.054\,(\text{Thrombolysis [yes=1, no=0]})-1.185\,Log_{10}\,(\text{copeptin [pmol/L]})}}$
Examples
The CoRisk online calculator and an Android app are available.[14,15]
A 75-y-old patient with an NIHSS score of 7 who received no thrombolysis and had a copeptin blood level of 11.0 pmol/L has a 46% probability of unfavorable 3-mo outcome.
The same patient with a copeptin blood level of 110.0 pmol/L (10-fold higher) has a 74% probability of unfavorable 3-mo outcome.

Abbreviations: CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients; NIHSS = NIH Stroke Scale.

The THRIVE score was derived among patients from 2 single-arm trials testing a thrombectomy device (MERCI and Multi-MERCI), and was externally validated in the MERCI registry.[16,17] In addition, THRIVE was validated in a cohort from the National Institute of Neurological Disorders and Stroke tissue plasminogen activator trial, which compared intravenous thrombolysis to placebo among patients admitted within 3 hours of stroke onset.[18] In all 3 studies, as the THRIVE score increased, the chances of a good outcome decreased. Increased chances of a good outcome were associated with vessel recanalization and use of intravenous thrombolysis. Thus, there are 3 groups of stroke patients in whom THRIVE has been validated: patients receiving endovascular treatment, patients receiving intravenous thrombolysis, and patients receiving no intravenous therapy despite qualifying for it (according to the National Institute of Neurological Disorders and Stroke tissue plasminogen activator randomization protocol). The last group, however, does not reflect everyday clinical practice because we do not withhold intravenous therapy in patients qualifying for it. Instead, in clinical practice, we withhold intravenous thrombolysis because of delayed hospital admission (i.e., beyond the time window of 3–4.5 hours) or contraindications (e.g., international normalized ratio >1.7). Therefore, in clinical practice, the THRIVE score cannot be applied to those stroke patients who receive no recanalization therapy, that is, the majority of all stroke patients. On the other hand, the CoRisk score addresses this need because it has been validated for stroke patients admitted within 24 hours of stroke onset. The CoRisk score can be applied to that majority of stroke patients who receive no recanalization therapy and allows computation of their chances of unfavorable outcome. While prognostic scores have been derived and validated for patients treated with thrombolysis (DRAGON,[19] SEDAN,[20] SPAN-100[21]), the CoRisk score applies to a broader range of stroke patients admitted within 24 hours from stroke onset, treated with or without thrombolysis.

Table 4 Sensitivity and specificity of copeptin blood levels for unfavorable functional outcome[a] at 3 months

Copeptin cutoff, pmol/L	Sensitivity, %	Specificity, %
Derivation cohort (AUC = 0.71)		
≥7.32	80	39
≥19.60	49	80
Validation cohort (AUC = 0.71)		
≥7.32	84	40
≥19.60	65	70

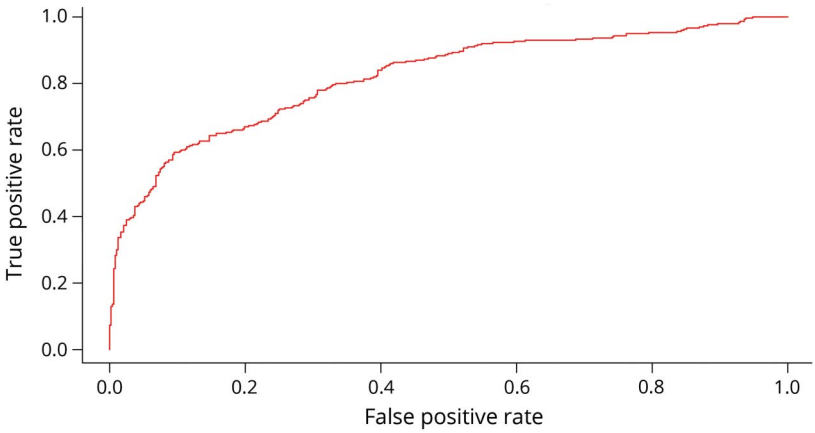
Abbreviation: AUC = area under the curve.
[a] Unfavorable functional outcome at 3 months was defined as a modified Rankin Scale score of 3 to 6, meaning disability or death.

Among the 8 assessed stroke prognostic scores, ASTRAL had the greatest prognostic accuracy.[3] For the derivation and validation of the ASTRAL score, the same definition of unfavorable outcome as for the CoRisk score, that is, mRS score of 3 to 6, was used.[22] The ASTRAL score is an integer-based score encompassing 6 items (age, NIHSS score on admission, stroke onset to admission time, range of visual fields, acute glucose, and level of consciousness). The ASTRAL score was derived in 1,645 patients from the ASTRAL (Switzerland) and was validated in 2 independent cohorts (Athens [n = 1,659] and Vienna Stroke [n = 653] registries). In the pooled validation cohorts, the AUC of the ASTRAL scores was 0.902, and the ASTRAL score was well calibrated.[22] When validated in the VISTA cohort, ASTRAL score achieved an AUC of 0.79.[3] Compared to the ASRTRAL score, the CoRisk score has 3 fewer items and does not include visual fields, which can be difficult, if not impossible, to assess in aphasic or somnolent patients.

The blood marker copeptin increases the prognostic accuracy beyond age, NIHSS score, and thrombolysis status, keeping the CoRisk score "lean" with only 4 items. The NRI for functional outcome in the current study (46%) is higher than the NRI reported in the original studies on copeptin (39.3%[5] and 11.8%[6]). The main reason is that, in the current study, we computed the continuous NRI as opposed to the categorical NRI in the original copeptin studies. For a prognostic tool such as the CoRisk score, we believe that any change in classification, even small ones, can be clinically meaningful to the patient and proxies, so we preferred not to specify any risk categories.

All items are suited for early prognostication, given the short incubation time of 30 minutes needed to assess copeptin plasma levels.[8] The pathophysiologic link between copeptin

Figure 2 Receiver operating characteristic curve of the CoRisk score for the prediction of unfavorable 3-month outcome

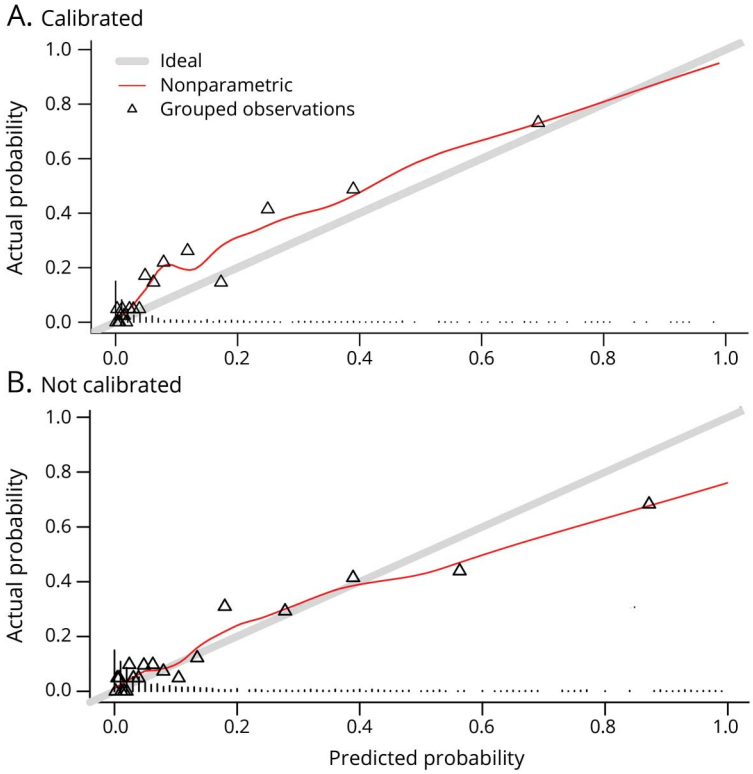


CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients.

and outcome is unclear. Copeptin, secreted from the hypothalamo-pituitary axis into the peripheral blood, acts as an "endogenous barometer of integral homeostasis."[23] Thus, copeptin assesses the severity of damage beyond age, measurable clinical impairment on admission, and ischemic lesion size.[23]

For outcome prognostications, validated scores perform better than clinicians.[24,25] A recent study compared the ASTRAL score to estimates of 244 clinicians with expertise in stroke for 720 real stroke scenarios for the prediction of 3-month mRS score of 3 to 6 in the general ischemic stroke population.[25] Overall, 86.5% of ASTRAL-based estimates were accurate, as opposed to 56.8% of estimated by clinicians with expertise in stroke. The majority of the physicians' inaccurate estimates (n = 231, 76.0%) were overly pessimistic, that is, overestimated the probability of unfavorable outcome

Figure 3 Calibration curves for the original model and recalibrated model (CoRisk score) for the prediction of 3-month mortality



(A) Calibrated and (B) not calibrated. CoRisk = Copeptin for Risk Stratification in Acute Stroke Patients.

at 3 months. Wrong prognostication misleads patients and their relatives, compromises end-of-life decisions, and undermines a cost-effective allocation of health care resources.

The Clinician Judgment Versus Risk Score to Predict Stroke Outcomes (JURaSSIC) study compared the iScore to the estimates of 111 clinicians with expertise in stroke for the prediction of death or disability at discharge (mRS score 3–6) in 1,415 representative stroke cases.[24] While 90% of the iScore-based estimates were within the 95% CI of observed outcomes, only about 1 in 6 clinicians (16.9%) was accurate for the prediction of death or disability at discharge. Here, clinicians tended to be overly optimistic, and vascular neurologists were not significantly more accurate than internists, emergency physicians, or general neurologists. Nearly half of the clinicians (48%) did not accurately predict the probability of the primary outcome in any of the 5 rated ischemic stroke scenarios.[24]

The CoRisk score has strengths and limitations. Strengths of the CoRisk score are the derivation and validation in 2 chronologically and geographically independent, large cohorts and the elevated prognostic accuracy despite having only 4 variables, all easily accessible in the emergency department. While brain imaging, including advanced modalities such as perfusion CT and MRI, provide information linked to outcome (e.g., infarct core size, tissue at risk), using a blood marker for prognostication has distinct advantages. First, the copeptin assay is available around the clock, whereas this is not the case for advanced imaging modalities in many emergency departments. A point-of-care tool for copeptin blood levels could shorten the turnaround to seconds. Second, copeptin blood levels can be easily interpreted through an online calculator to compute the validated CoRisk score, while the interpretation of brain imaging for prognostic purposes is more cumbersome because it considers not only infarct core size but also its neurotopographic location. Third, the costs of the copeptin assay are lower than those of urgent brain imaging, including its interpretation for prognostic aims, a task requiring highly skilled professionals. A limitation of the CoRisk score is the lack of validation for mortality prediction, which may be due to the low numbers of deaths along with different practices on withdrawal of care between the derivation and validation cohort. This may explain why the NRI for mortality was accurate in the original cohorts, as opposed to the current study in which findings from the derivation cohort are translated to the validation cohort. Because we did not collect data on do-not-resuscitate orders, we were not able to explore this hypothesis. Another limitation is the baseline differences between the derivation and validation cohort, which may have contributed to a higher proportion of unfavorable outcomes in the derivation cohort (+5 percent points). In particular, in the derivation cohort, the following baseline characteristics can explain the higher proportion of unfavorable 3-month outcomes: higher age, lower thrombolysis rate, and higher Charlson comorbidity index score. Such differences are likely to be inherent to the 2 cohorts, which were chronologically and geographically independent. The external validation of the CoRisk score despite such differences argues for its applicability to predict 3-month functional outcome among patients with an acute ischemic stroke. Finally, the CoRisk score is not a tool to select patients for thrombolysis or endovascular treatment because the CoRisk score was not developed to predict vessel recanalization, a crucial outcome predictor after thrombolysis.[26]

Further prospective studies should assess the prognostic accuracy of copeptin in the context of other biomarkers. In addition, future studies should unravel whether the association between copeptin blood levels and stroke outcome is only an epiphenomenon or whether it reflects a causal relationship. The CoRisk score is a novel biomarker-based, ready-for-use, parsimonious, validated score for the prediction of disability at 3 months after an acute ischemic stroke.

Author contributions

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